REMARKS

Claims 1 to 5, 7 to 20 and 21 to 39 are pending in this application.

35 USC §112, Second Paragraph Rejection

Applicants would like to thank the Office for the withdrawal of this rejection against claim 37 per Advisory Action of May 15, 2008.

35 U.S.C. §103 Rejection

In paragraph 7 and 8, on pages 7 to 15 the Office continues to reject claims 1 to 5, 7 to 9, 11 to 12, 19 to 20, 22 to 24, 26 to 33 and 36 to 37 under 35 USC §103(a) as being obvious over Uhlmann et al. (Electrophoresis, 1999) (hereinafter "Uhlmann '99")) in view of U.S. Patent 6,258,568 to Nyren et al. (hereinafter "Nyren").

The Office stated that Uhlmann'99 teaches a method for identifying methyl cytosines comprising treating a sample containing genomic DNA with sodium bisulfite and amplifying the sample by PCR. The Office further stated that Uhlmann '99 teaches that the amplified nucleic acids were sequenced by the dideoxynucleotide chain termination method to determine the methylation state of the amplified product.

The Office conceded again that Uhlmann does not teach a method wherein the amplification primer has a label that forms an anchor for removal of single stranded amplified nucleic acid molecules.

The Office also acknowledged that Uhlmann does not teach that the amplified nucleic acids were sequenced using a real-time sequencing method.

However, the Office expressed the opinion that these teachings are provided by Nyren.

In particular, the Office expressed the opinion that Nyren teaches that one or more of its PCR primers may carry a functional group such as a biotin which permits subsequent immobilization (col. 8, lines 22 to 31) and that real-time sequencing provides a wide variety of desirable advantages.

The Office concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann '99 by using pyrosequencing to determine the sequence of the amplified DNA fragment as suggested by Nyren.

THE OFFICE HAS NOT PRESENTED A *PRIMA FACIE* CASE OF OBVIOUSNESS

As discussed in applicants' previous communication, the Office noted that Uhlmann '99's amplification primers are not detectably labeled. Uhlmann '99's amplification product is cloned to produce single stranded DNA. This cloning, follows Unhmann '99's amplification and precedes the sequencing. ("[P]lasmid DNA of positive clones . . . were sequenced by the dideoxynucleotide chain-termination method." (see 2.5, pages 1751 and 1752)).

As noted, claim 1 recites:

(b) amplifying said nucleic acid molecule . . . via at least one amplification primer . . . detectably labeled with a detectable label that forms an anchor for removal of single stranded amplified nucleic acid molecules to generate a single stranded amplified nucleic acid. . . *[emphasis added]*

Claim 12 contains similar language.

Applicants previously submitted that the person skilled in the art would be reluctant to make the modification to Uhlmann that the Office suggested, namely detectably label Uhlmann '99's amplification primers as it would interfere with Uhlmann '99' s subsequent cloning step. Applicants noted that, for example, U.S. Patent 6,589,736 to Rothschild et al. discloses in its background section, "PCR products that are biotinylated are not suitable material for cloning." (col. 7, starting on line 23). The same patent states also in col. 34, starting on line 40 that "the presence of biotin on the nascent DNA can interfere with its subsequent utilization in cloning or hybridization analysis."

Thus, applicants noted that modification proposed by the Office would render Uhlmann '99 unsatisfactory for its intended purpose (see MPEP §2143.01, V.)

In response, the Office stated on page 17, first full paragraph, of the February 28, 2008 Office Action:

> **"First of all, the claims do not require a cloning step. Uhlmann teaches amplifying a nucleic acid sample, cloning the amplification product followed by sequencing. However, Nyren's method eliminates the need for a cloning step since Nyren teaches that the sequencing step can be performed on PCR amplified fragments (col. 7, l. 65 to 67)."**

The Office essentially repeated this argument in the Advisory Action of May 15, 2008. Applicants would like to point out again that *In re Gordon's* analysis looks at whether the suggested modification would render the **prior art device/method** unsatisfactory for its intended purpose. The analysis does not look at whether the suggested modification would render the claimed invention unsatisfactory for its intended purpose. It is also noted, that, among others, claim 48 does require detectably labelling the amplification primer as highlighted above.

Thus, applicants note that an obviousness analysis starts out at the prior art, not at the claimed invention. The question is, whether it would have been obvious to combine and/or modify the prior art to arrive at the claimed invention.

One widely accepted indicator that a modification would not have been obvious is, as applicants pointed out, that the modification proposed would render the reference, here Uhlmann '99, unsatisfactory for its intended purpose.

MPEP §2143.01, V. to which applicants referred previously, cites *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984): In *In re Gordon*, the claimed device was a blood filter. The prior art taught a liquid strainer for removing dirt and water from gasoline. The Board concluded the claims were *prima facie* obvious, reasoning that it would have been obvious to turn the reference device upside down to arrive at the claimed invention. The court reversed, finding that if the prior art device was turned upside down it would be inoperable for its intended purpose because, among others, the gasoline to be filtered would be trapped.

In re Gordon is a clear example, that the "intended purpose" to be considered is that of the device/method of the prior art reference, not that of the claimed invention, as the Office seems to suggest (see cite above).

Here, rather than turning the device around (*In re Gordon*), the Office, while citing Uhlmann' 99 as teaching the amplification required by the presently claimed invention, suggests, in order to arrive at the claimed invention, to label Uhlmann '99's amplification primer in a way that would render Uhlmann '99 inoperable for its intended purpose.

In view of the above, applicants respectfully submit that the Office's analysis does not support a *prima facie* case of obviousness. For the Office's convenience, applicants include a copy of *In re Gordon.*

In this context, applicants would also like to direct the Office's attention to a recent discussion of non-obviousness in *Ortho-McNeil Pharmaceutical v. Mylan Labs,* 2007-1223, Fed Cir. March 31, 2008.

The court in *Ortho-McNeil Pharmaceutical* explains on page 11, "the flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case. In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention."). The TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence – teachings, suggestions (a tellingly broad term), or motivations (an equally broad term) – that arise before the time of invention as the statute requires."

In particular, Judge Radar notes*:* "In retrospect, Dr. Maryanoff's pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." (page 10)

This decision, which is also attached for the Office's convenience, and Judge Rader's observations tie in well with applicants further arguments of non-obviousness set forth in applicants January 17, 2008 response, which the Office, however, left uncommented up to the Advisory Action of May 15, 2008.

THE OFFICE DID NOT CONSIDER ALL OF APPLICANTS' ARGUMENTS OF NON-OBVIOUSNESS

In particular, applicants submitted an exchange between John Dixon and Karl Voss (1996) discussing technical difficulties (Fed. Reg. Vol. 72, No, 195, p 57534, right column) associated with using biotinylated primers which was attached to the response of January 17, 2008 as "Biotin-PCR-primers".

Furthermore, applicants pointed out that additional technical difficulties flowing from the suggested combination of Uhlmann '99 and Nyren could have been expected to flow from the complexity of the reaction mixture used for pyrosequencing. This mixture is considerably more complex than the dideoxynucleotide chain termination sequencing mixture used, e.g., in Uhlmann '99. The effects of a chemical modification of the DNA as

used in Uhlmann '99 and any residual chemicals were unclear at the time the invention was made.

In the Advisory Action, the Office pointed out that one failed attempt by one person does not indicate that other people would fail as well. This might be true. However, technical difficulties that others experience are relevant with regard to motivation to make a modification. For the relevance of the argument the Office is referred to the wording of claim 48 as highlighted above.

The Office also expressed the opinion that applicants' argument regarding uncertainties associated with the use of complex reaction mixture of Nyren subsequenct to DNA modification does not provide any evidence as to unexpected results. The fact that substances such as certain chemicals or other substances can interfere with subsequent reactions is well known and is evidenced, e.g., by Nyren, col. 7, third full paragraph. This is particularly true if the subsequent reaction involves complex reaction mixtures. The record also reveals that Nyren's method involves more complex reaction mixtures than the method disclosed by Uhlmann '99 to follow the DNA modification. These facts are relevant with regard to obviousness since they reflect on the willingness, ergo motivation, of a person skilled in the art to make a respective modification in view of these facts.

"In retrospect, [the] . . .pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." *Ortho-McNeil Pharmaceutical v. Mylan Labs,* 2007-1223, Fed Cir. March 31, 2008 at page 10.

THE OFFICE DID NOT CONSIDER ALL OF THE CLAIM LIMITATIONS OF CLAIM 12: FINALITY OF THE OFFICE ACTION

With regard to claim 12, the Office again explains on page 17 and 18 that it views the preamble as an intended use statement. However, applicants referred in their argument of January 17, 2008 clearly to the body of the claim, in particular to limitation (d), not the preamble. Applicants stated on page 22 of the January 17, 2008 reponse:

> "With regard to the Office's statement regarding the preamble of claim 12, applicants would like to point out that **subsection (d)**, irrespective of the weight given to the preamble of the claim, is part of this claim and should be considered by the Office. As the MPEP §2143.03

points out, a claim limitation should be considered even if the Office believes such a limitation indefinite ("[A]ll the limitations of the claims must be considered and given weight" *[emphasis added]).* Applicants can find no indication on pages 10 to 13 of the Office Action how **this claim limitation** is made obvious by the combination of Uhlmann '99 and Nyren to support a *prima facie* case of obviousness and notes the Office's statement made in context of the discussion of dependent claims 13 to 16, 18 and 38 on page 16, third paragraph." *(emphasis added)*

For the Office's convenience claim limitation (d), which follows the transitional phrase of the claim, is reproduced below:

> "(d) detecting whether said nucleotide is methylated or not methylated at said predetermined position in the sample to diagnose said pathological condition or the predisposition for said pathological condition."

In the Advisory Action, the Office did, for the first time, comment on applicants non-obviousness argument with regard to this limitation (which is clearly not part of the preamble), arguing that the phrase including and following "to diagnose" is an intended use that was not considered by the Office and even if it would have been considered, that it was obvious in view of the art of record. Applicants submit that the fact that the phrase including and following "to diagnose" was not considered a limitation should have been raised earlier to provide applicants an opportunity to amend the claim prior to issuance of a final Action. The Office is referred to MPEP §706.07 and 37 CFR §1.113 regarding the finality of an Office Action where a clear issue has not been developed.

CLAIM 39

With regard to new claim 39, the Office stated that:

"Newly presented claim 39, modifies further limits claim 34 by stating that the standard deviation is not more than 1%, however, again the claims do not actually require a step of detecting an allele frequency of 5% that is detected with a standard deviation of not more than 1%."

Applicants noted that claim 39 states:

> "wherein the allele frequency of 5% is detected with a standard deviation of not more than 1%." (*emphasis added*)

While applicants previously submitted that claim 39 in its previous form does require a detection of an allele frequency of 5% and still believe that this would be indeed the case, applicants have now rewritten the claim to be dependent on claim 10 to

remove any potential reference to a capability. Applicants also submit that the term "can" in claim 37 expresses a capability and not an option (MPEP §2106, II, C.).

OTHER ISSUES

Turning to the Office's statements in paragraph 11 of the Office Action regarding references submitted tending to show "praise by others", applicants submit that the statements made in publications can hardly be considered "argument of counsel" as they are part of written statements by third parties. To clarify the record, applicants submit a declaration by one of the inventors, namely Karen Uhlmann, stating that the content of the documents provided was not produced at her request nor, on information and belief, at the request of one of the co-inventors.

To reduce the issues in this case, applicants also attach declarations by Heide Ritter and Mohammad Tolliat that explain their contribution to several pieces of information submitted to the Office on February 21, 2006 and subsequently considered by the Office. These declarations were not presented earlier as the Office did not raise, subsequent to the consideration of these references per Office Action of March 14, 2006, any issue regarding the same. As these references were already reviewed by the Office and the declarations were provided by co-authors of the respective pieces of information, the declarations, require, at best, a cursory review.

Again, the undersigned sincerely urges the Office to call her at the number provided below to discuss this case.

No fee is believed to be due. However, the Commissioner is authorized to charge or credit deposit account no. 50-3135 as required.

Respectfully submitted,

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